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Evaluation of Quality of Life of Childhood Cancer Survivors: A Methodological Conundrum

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INTRODUCTION

Cancer alters children's lives in myriad ways, beginning at diagnosis and continuing well beyond completion of therapy. Some effects are related directly to the physical course of the disease and treatment: the etiologies of other effects are less clear. Decrements in physical functioning may be secondary to toxicities of treatment, physical symptoms, or decreased motivation and energy. Psychosocial sequelae, such as diminished school achievement and social competence, may be the result of neuropsychological deficits from chemotherapy toxicity or they might be created by the social and academic isolation imposed by the cancer therapy. The reports of neuropsychological and psychological sequelae in children with cancer vary in part due to different diagnoses and patient ages. Nevertheless, it is clear that pediatric cancer survivors are at a much greater risk for impaired functioning than the normal population [1,2].

Specific deficits in cognitive and emotional status are identified frequently in children with cancer. These effects are generally noted in relation to school achievement. Studies suggest that children with cancer have a much higher frequency of school-related problems (fourfold increase) than normal, healthy children [3–5]. Children treated for leukemia were reported to have lower school attendance, poorer concentration, underactivity, less energy, greater inhibition, less willingness to try new things, less emotionality, and delay in skill development compared with other children [6]. In a study of long-term psychological effects of leukemia, 50% of the children showed learning problems (despite normal IQ) at 5-year follow-up, and 61% displayed poor or very poor concentration and/or short attention [7]. In another study of long-term childhood survivors of acute lymphoblastic leukemia (ALL), although the proportion of survivors who enjoyed normal health was similar to the proportion found in the Canadian general population, 33% of the study population reported subnormal levels of cognition, and 28% reported subnormal emotional functioning [8]. Psychological adjustment is relatively independent of traditional measures of morbidity, but is strongly related to functional status and days missed from school. Children tend to underreport symptoms of depression, but it has been shown that levels of depression are associated with hospitalization and increasing time since diagnosis [9].

These preliminary studies demonstrate conclusively that pediatric cancer survivors often bear significant functional morbidities that compromise their ability to resume normal, productive functioning. It is of note, however, that these social, emotional, and role dysfunctions often persist even in the setting of good to superior clinical health. The opposite may also be true: aspects of functioning are preserved even in the setting of moderate organ impairment. Given the divergence between ''objective'' clinical status and functional status, reliance on either aspect to the exclusion of the other may fail to capture the spectrum of survivors' experiences.

Dozens of studies testify to the magnitude of clinical and functional morbidities endured by pediatric cancer survivors. This population is clearly at risk for multiple problems, ranging from chronic poor health to emotional or social dysfunction. However, although these studies have been invaluable in initiating discourse on the needs of survivors, outcomes assessment of pediatric cancer survivors is relatively immature and is still quite fragmented in approach. Much of the research is unidimensional, focusing on specific, solitary deficits at the exclusion of all other concurrent deficits. This type of research does not explain the complexity of an individual survivor's experience or the ways in which an individual's functionality is defined by the amalgamation of many different domains. This overall balance of function and dysfunction defines for an individual their quality of life. Thus, to truly understand the long-term outcomes (QOL) for pediatric cancer survivors, research must examine simultaneously all of the factors that are considered to be of influence. Only then, with comprehensive, multi-dimensional assessment and an understanding of dynamic functional trade-offs, can survivors' overall QOL be ascertained. Ultimately, this broader definition of outcome will redirect the way in which clinicians par-

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ticipate and assist in a patient's acclimation to living with cancer, both immediately and with regard to future potential. The ramifications are enormous, impacting not only on therapeutic interventions but also on utilization priorities, health policy, and resource allocation. This paper summarizes the two-tiered methodological challenge in measuring QOL in pediatric cancer survivors–a challenge that is defined by the age of the respondents as well as the disease.

CHILDREN'S ISSUES IN QUALITY-OF-LIFE RESEARCH

The methodological development of an appropriate, disease-specific, QOL instrument for the assessment of pediatric cancer survivors parallels the development of adult oncologic measurements in construct; in application, however, the two populations differ enormously. Childhood provides an entirely different context within which disease and treatment are experienced. Therefore, for children, a primary methodological goal is not so much the reestablishment of appropriate disease-specific domains but, rather, the accessibility and valid interpretation of children's responses. In the absence of this understanding, the qualitative values of children's responses is meaningless. The choice of study paradigm, therefore, must account for the pediatric setting.

The general domains that are recognized commonly in both adult and pediatric QOL analyses include physical function, role function, social/peer function, and emotional well being. Although these domains may be rated on the same continuum, the factors that define an individual's QOL may be different in the two contexts. Some scales of physical function that are used in the adult population, for example, are based on levels of independence or required assistance. Children, by nature, have a lower baseline of independence: requiring assistance is less of a marker of severity. Similarly, children's role function is dictated by the roles they engage in (as displayed by school participation or family interaction). Levels of functioning in school (and/or variations in these levels) are different from levels of functioning in a workplace, reflecting different expectations or requirements for ''successful'' involvement. Children's social groups and patterns of social involvement are also very different from those of adults, reflecting both different social roles and different social investments. Emotional well being is correlated to children's perceptions of themselves and their perceptions of normal ''successful'' attainment of functional goals: both function and perception of function are influenced by cognitive and developmental maturity (which dictates both actual attainable parameters and perceptions of self location within those parameters).

Pediatric QOL assessment must incorporate the specific needs of children. This is done both by modifying evaluated domains to recognize the unique functional and emotional context of childhood and by using instruments that are sensitive to children's parameters of functioning, as dictated by their developmental and cognitive evolution. Specifically, pediatric assessment demands the use of instruments that are developed for children. Although the central domains that are being tested may be the same for adults and children, the applicability to each is different: questions that bear little relevance to a subject's life will render scores of little value.

In addition to the qualitative solidity of instrumental development/selection, quantitative methodological issues must be considered. These include the mode of administration, selection of an appropriate respondent, scope of measurement, timing of assessment, and valid interpretation of the results. All of these issues are affected by the limited accessibility of the pediatric population, which is delineated specifically by children's developmental variability and intellectual evolution.

The mode of administration used in QOL measurement is dependent, in part, on the respondent who is being questioned. Mode of administration pertains to whether an interviewer administers the instrument or it is self administered. Self administering the instrument tends to be preferred, because it both reduces research staff burden and, more importantly, eliminates interviewer bias and/or administration variability. The suitability of self-administered measures in a pediatric population is controversial, with the debate centering around the age at which children are intellectually/cognitively capable of self sufficiency for testing and whether their responses are valid and reliable. This is certainly related to the complexity of the instrument and the questions that are being asked. Most pediatric instruments are administered to a proxy respondent (parent, teacher, physician) who is thought to understand the needs and concerns of the child within a current and future context.

The appropriateness and validity of proxy reporting is speculative [10]. Clearly, as dependents, children are represented by a decision maker, often a parent (or parents), who is ultimately responsible for clinical evaluation and who may have unique perceptions of QOL independent of the child's and the physician's perceptions.

Whereas decision-maker input is incontrovertibly important, the validity of proxy reporting as a true measure of child function is contested. Considerable variability has been found between observers/respondents (physicians, nurses, parents, teachers, and children) in the assessment of morbidity, psychosocial function, and emotional function [11,12]. Parental reporting is often divergent, perhaps due to parents' protective and/or idealized expectations for their child or the convergence of their own subjective experiences with the perceived experiences of their child [13,14]. The issues become hazy.

Reports indicate that children's QOL is often correlated strongly with parents' sense of their own levels of support as well as their own socioeconomic status, education, and emotional function [15,16]. These findings highlight the potential significance of family dynamics of children's function: some responses might be artifacts of parental proxy reporting in which the parent transfers his/her own sense of debilitated function to the child.

The choice of respondent influences the scope of measurement. Respondent validity is important in determining which scope is appropriate. Responses to objective questions, such as clinical severity or school performance, are most likely to be accurate regardless of observer, whereas the answers to subjective questions about anxiety, body image, or social dynamics are likely to be less valid when received by proxy reporters [10]. If parents or physicians are respondents, then the scope of measurement should be limited to domains that are respondent-valid: instruments that are global and proxy-reported should be generalized (as opposed to in depth) to avoid the greater respondent discrepancies that are associated with subjectively influenced details. Aggregated scores compound this respondent variability by aggregating the error of margins for each domain. The resultant total error margin can mask the actual delicate differences between domains.

The timing of assessment is an important consideration for pediatric research. Studies may be cross sectional or longitudinal. Clearly, determining the timing of assessment is dependent on the overall purpose of the study and the availability of suitable measures. Chronic illness outcomes research mandates longitudinal testing to capture the dynamics of an illness with multiple sequelae spanning a range of time. Cross-sectional research facilitates the accumulation of larger numbers of subjects and is appropriate for the assessment of a finite outcome at a fixed point in time. Cross-sectional studies do not offer causative or comparative data (from baseline to endpoint) for an individual patient, but they can be used to establish general trends in the population.

Both types of studies, longitudinal and cross-sectional, pose unique methodological considerations that are driven by the progressive cognitive and emotional development of childhood. Cross-sectional studies must be careful to define the study paradigm so that they can limit the variability imposed by the subjects' developmental staging. Longitudinal studies are more robust, because comparisons can be made between developmental stages. Particularly within chronically ill populations in which illness may span several developmental stages of growth, it is important to see how development impacts on QOL. Cognitive and intellectual maturity, as discussed above, defines not only functional roles but also the ways in which those roles are perceived (distinction and interaction between self and others). This directly influences a child's perception of QOL. It is possible that, even if external variables remain constant, a child will perceive things differently at each developmental stage. Longitudinal assessments may clarify whether development influences a child's QOL (clinically and cognitively) and whether developmental shifts are based purely individually or exist across the population.

CANCER QUALITY-OF-LIFE RESEARCH

QOL postcancer is complex and multi-factorial, reflecting the wide range of different diseases (and concomitant patient experiences) that constitute the cancer population. Like in all QOL research, the primary challenge is to identify the primary domains of QOL as valuable by clinical, functional, and emotional status. Cancer-specific research must then examine the specific debilities that are associated with cancer that drive patients' health status. Studying this population is complicated by the expansive parameters of the definition of cancer. ''Cancer,'' as a descriptive variable, is used to characterize an underlying malignant process, but the term does not designate the specific clinical and functional deficit/symptoms that the malignancy produces (the specific disease). The cancer population, although it is unified by the broad diagnosis, is distinctly stratified by the specific diseases. QOL research within the cancer population must address the separate issues created by both the broad cancer diagnosis and the specific disease presentation. Both aspects contribute to the actual function and QOL of cancer patients. The former has primarily psychosocial repercussions that concern mortality, social stigma/stereotype, and having a long-term, often incurable illness. The latter involves the clinical, functional, and psychosocial sequelae of the actual disease course and treatment.

Considering the complexity created by this population's diversity, the methodological question becomes one of construct. What are the appropriate QOL domains, and what is the best approach to the measurement of these domains? [17]. The consideration of an instrument's construct may be broken down into three methodological criteria: face validity, content and/or construct validity, and reliability [18].

Face validity is a measure of the common sense of an instrument. Do the tests selected, the questions asked, or the measurements taken seem to be related logically to the phenomenon being measured [19]? Face validity can testify to the completeness of the instrument. It is important that a QOL instrument encompasses all of the central aspects of patients' experiences that might influence global QOL. In relation to cancer research, this means

that an instrument must be multi-dimensional and must specifically address and distinguish generic, disease-specific, and diagnosis-specific aspects of functional status. Each exerts an important and distinct influence on total QOL. The establishment of face validity must also consider the applicability of the respondent. Different observers have different perspectives. Some may be more (or less) qualified than others to answer specific questions. The comprehensiveness of an instrument is limited by the limitations of the respondent. Thus, face validity dictates both the scope of measurement and the choice of respondents.

Content and construct validity is a measure of the intrinsic value of the instrument; that is, does the instrument intrinsically measure what it is supposed to measure? This is the quantitative backbone of qualitative assessment. When looking at a global or summary score of QOL, it must be clear that the sum represents accurately the synergistic and individual contributions of the influencing parts. If this is true, then there should be little unexplained variability in the test analysis. Good content validity ensures that the score of a domain describes accurately a subject's function and is therefore capable of distinguishing differences between subjects (sensitivity). An instrument's ability to discriminate between individuals within one population is of critical consideration for the comparison of patients within the cancer population.

Reliability is a measure of consistency, or how consistently respondents score questions of equal or similar value or both at a given time and over time. Reliability has implications for both the instrument design (internal consistency reliability) and the instrument's efficacy in serial application (test-retest reliability). These two types of reliability function independently. In design, internal consistency reliability can refer to the concordance between scores within a domain. For example, when a respondent is asked different questions all within the same domain, the scores should coalesce to indicate the same general trend and direction. Therefore, a respondent who scores high for running should also score high for walking–they both indicate physical function. Similarly, scores should be reliable at different time points (test-retest reliability). If a respondent scores high for running at time A, then he or she should also score high for running at time B, *provided* that clinical states and/or influencing variables have not changed or been manipulated. In populations with dynamic, varying clinical courses, respondents' scores will change over time commensurate with the changes they experience clinically. Therefore, whereas internal consistency reliability may remain intact, test-retest reliability may vary with the shifting clinical state. When an instrument is developed for use within a clinically dynamic population, the instrument's test-retest reliability must be determined initially by controlling for sources of variation. Once reliability has been established, the instrument may be used with confidence to capture accurately the true course of respondents' variable experiences.

The consideration of timing and clinical status is particularly germane to oncology research given the variability of the clinical course during and after cancer therapy. Patients' issues during therapy in the acute phase tend to be very different from their issues in the long term, reflecting the transition from acute concerns for mortality and treatment-induced morbidity to long-term concerns about normalcy and reintegration into normal functioning. The development of a study paradigm for the oncology population must consider these key transitions in health states and experiences: the study question must be articulated clearly to address these differences across time within the population. There are two ways in which a study may examine the influence of time on clinical status. Individual patients can be surveyed at several points over time (longitudinal study), or a randomly distributed sample of the patients may be surveyed at one time as a snapshot of time across a population (cross-sectional study). The advantages of the cross-sectional snapshot often include access to a large(r) population and the ability to conduct the assessment in a relatively shorter research window. The most striking disadvantage is that patients will be in the treatment and/or recovery period at variable times. The interpretation of results from a cross-sectional study must be made judiciously, because it is so dependent on case mix. The longitudinal study allows for intra-reporter comparison across time as well as linkage to the clinical state.

The pediatric oncology literature to date has approached these issues from many different perspectives. Whereas many researchers have relied on the use of the limited standardized (or not standardized) instruments, some investigators have developed instruments specifically for the purpose of analyzing QOL postcancer. These efforts have been thwarted by a number of methodological obstacles: the need for (and the apparent lack of) a comprehensive identification of QOL domains; the development of a tool that is global enough to address and discern issues across the whole population and, yet, that is sensitive to the subtle differences within disease groups; and the extensive standardization needed to ensure reliability and validity. QOL research for adult oncology has overcome these methodological hurdles and may serve as a template in the evolution of comprehensive, multi-dimensional, disease-specific, QOL instruments for pediatric oncology.

Historically, the difficulty in assessing more multidimensional, cancer-specific QOL has been hallmarked by the inability to reach a consensus about what dimensions are of importance. This lack of definition has stymied the development of new, more disease-specific, domain-

appropriate instruments. Consequently, much of the early research relied on more generalized, health-related, QOL instruments that were developed for use within the general population. The benefits of using generalized instruments for a disease population is that the scores may be compared with the standardized norms of the general population. In this manner, differences between healthy and ill populations may be identified, clarifying domains that are affected by disease.

In the adult population, some generic but multidimensional instruments that are used commonly to assess health-related QOL include the Short-Form-36 (SF-36) [20–21], the Sickness Impact Profile (SIP) [22], and the Psychosocial Adjustment to Illness (PAIS) [23]. All three were developed specifically to address illness-related dysfunction. Each assesses a broad scope of domains (including social, emotional, and role functioning, well-being, and treatment satisfaction), which have been validated extensively. It is of note that the SF-36 was specifically designed and validated for use with chronically ill populations, suggesting a heightened sensitivity to disease-specific issues and a limitation to assessing outcomes that are important to chronically ill patients. The primary drawback for these instruments' application in the cancer population is the lack of disease-specific questions.

The analogous generic instruments that are used within the pediatric population are less comprehensive and tend to be oriented more around mental health and behavioral adjustment. Commonly used instruments include the Child Behavior Checklist (CBCL) [24], the Personal Adjustment and Role Skills Scale (PARS) [25], and the Health Resources Inventory (HRI) [26]. Although none of these was designed specifically to assess chronically ill populations, each has been used for that purpose. The primary drawback of these instruments is the lack of multi-dimensionality. The CBCL is a parent-report that was designed to assess social competencies and behavior problems in children 4–16 years of age. It may be used in conjunction with reports from teachers and children (11–18 years of age). It is of note that the CBCL has extensive gender- and age-specific standardization. However, although the CBCL has met with success in identifying behavioral differences between ill versus healthy pediatric groups, the instrument is not necessarily appropriate for evaluation within groups. The CBCL was designed to identify pathological differences, but is not sensitive to the subtle differences within a group [27]. The PARS, which is used to assess overall psychosocial adjustment of children 5–18 years of age, is similar to the CBCL. The PARS, however, has been validated within a group of chronically ill children. The HRI is perhaps the most sensitive of the three instruments to the dynamics of chronic illness. It is a parental rating of a child's psychological adjustment and resilience in meeting new tasks and challenges. The HRI addresses more subtle differences in competence rather than pathological deviance, which may make it more applicable to evaluations with a chronically ill population. None of these instruments, however, is disease-specific, and none was designed with regard to physical confounds. Test items measure performance and accomplishments rather than functional capacity. Often, chronically ill children are limited in their activities but are still functionally competent. The overlap between what is physical versus psychological is sometimes cloudy, leading to inaccurate scoring on a purely psychological evaluation.

Generalized tools are useful for the comparison of individuals to the general population. It may be inappropriate, however, to assume that cancer patients exist within the same context as the general population. Cancer patients' lives are very different from those of normal individuals due to the enormous physical and emotional burdens that cancer survivors must endure. Thus, the significance and value of experiences/healthstates/compromise in functioning for the cancer patient may be markedly different from generalized population norms. The information gathered must be sensitive to differences within the disease population.

Several multi-dimensional, disease-specific questionnaires have been developed and validated specifically for use within the adult cancer population [28]. Four well-known instruments are the Functional Living Index-Cancer (FLIC) [29], the Functional Assessment of Cancer Therapy (FACT) [30], the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core (EORTC-QLQ C30) [31], and the Quality-of-Life Index (QLI) [32]. Although they differ in some important ways, they all satisfy many of the criteria discussed above for the development of a comprehensive oncologic QOL instrument. They are cancer-specific, with the purpose of discriminating differences within the cancer population (within disease group); functionally oriented; multi-dimensional (including generic and disease-specific domains); sensitive to patients' changes longitudinally; and succinct and easy to administer (all but the QLI are self administered). The FLIC, the FACT, and the EORTC-QLQ C30 are similar in content. One disadvantage of using the FLIC is that it provides only a total QOL score, which prevents the analysis of individual domains, whereas the FACT, with its generic core and multiple, specific subscales, reflect issues or problems that are associated with different diseases, treatments, and symptom complexes. The FACT provides a total QOL score as well as scores for the different domains. The QLI is the most widely used observer-rated scale and was designed to be conceptually similar to the neonatal Apgar scale [33]. It provides a global score of QOL. Its strengths include easy administration and strong internal consistency. However, it is unclear how

sensitive it is to actual patient function: observer and patient ratings only show modest correlations.

QOL research in pediatric oncology has only just begun to feature comprehensive, disease-specific instruments comparable to those developed and validated in the adult field. To date, only one instrument has been validated. Goodwin et al. [34] recently reported on the development and validation of the Pediatric Oncology Quality-of-Life Scale (POQOLS), which is a parent-reported measure for assessing the QOL of children with cancer. This scale evaluates three factors: physical function and role restriction; emotional distress; and reaction to current medical treatment. The POQOLS is similar to the adult FLIC, in that it was designed specifically to assess the oncology population: it includes questions that are specific to experiences associated with cancer treatment. Initial analysis of the instrument offers preliminary support for the psychometric adequacy of the measurement (internal consistency and concurrent and discriminant validity). The questionnaire appears to meet important methodological criteria: it is comprehensive, easily administered, reliable, and valid. The primary drawback of the POQOLS is the omission of a child report. This raises questions regarding the instrument's sensitivity to the actual experiences of the pediatric patient. Further analysis is also needed to establish its validity longitudinally.

The multi-attribute health status survey (MAHS) [35] was also developed to assess QOL in children with cancer. The MAHS is multi-dimensional, including scales for sensory function, mobility, emotion, cognition, self care, pain, and fertility. Unlike the POQOLS, however, this instrument attempts to define functional capacity with scales similar to the Karnofsky Performance Index [36] and the Lansky Play Performance Index [37]. Scores are indicative of status at a point in time but not of overall function and/or determinants of function. The goal of this approach is to document the extent to which deficits in health status for each attribute inhibit or prohibit normal functioning rather than the level at which an individual chooses to function, as would be reflected in a measure of performance. The global health status of an individual patient at a point in time is described as a health state, which is defined by seven levels of function: one level from each of the seven attributes. The health-related QOL score for each global health state is calculated from a mathematical formula, which is called a utility function, that is developed from measures of preferences [38]. The strength of this instrument is clearly its ability to distinguish health state as a function of clinical severity. Used for serial evaluations, it can delineate changes in clinical status independent from the social and emotional changes that occur commensurate to progression in disease, treatment, or survival status. However, the MAHS is less capable of describing the dynamic qualities of patients' lives or the ways in which different attributes synergistically influence an individual's actual function. Also, initial analysis of this instrument shows significant divergence between the assessment of morbidity as reported by different observers. This variability in scoring mandates further analysis and/or the inclusion of multi-observer scoring.

APPLICATIONS OF QUALITY-OF-LIFE ASSESSMENT

QOL assessment may serve as a descriptor or predictor of outcome. QOL studies have been used to describe follow-up to a single treatment modality, such as bone marrow transplantation or in randomized clinical trials. Depending on the goals of the study and the suitability of the instruments selected, comparisons can be made within the study population by clinically relevant subgroupings or can be made with normative data from the general population to describe deviations in global or domain-specific assessments [35].

Alternately, QOL assessment has been used as a predictor of outcome. Several studies in the adult oncology population have demonstrated an association between patient-rated QOL and survival [39,40]. This relationship has also been described with physician-reported QOL by using the QLI [41]. In multivariate analysis, QOL scores, both global assessment and selected, domain-specific items (e.g., physical functioning), have emerged as independent predictors of enhanced survival. Information of current functional status has also been shown to predict future functioning as well as impact on utilization of services.

QOL assessment, if it is conceived and elicited properly, has the potential to offer additional and often complementary information on the patient's status. Clarity in the formulation of study goals, careful selection of study instruments, frequency of assessment, and attention to the details of reporter selection will ensure that the information realizes its potential in better informing physicians, patients, and policy makers about outcomes.

SUMMARY

QOL assessment in pediatric oncology is seriously understudied, especially compared with the adult population. The limited progress is due to the methodological complexity of the task, which should not be viewed as insurmountable. Given a precise study question, the methodological issues can be clarified simply, piece by piece. Researchers must consider very carefully the specific characteristics that define a study population in order to choose an instrument that is domain-appropriate and valid for the assessment paradigm. The first priority

should be that a researcher must identify the means of accessing the information of interest. In the pediatric population, information about children's status may be elicited from parents, medical personnel, teachers, or the children themselves. Clearly, the type of instrument to be used for assessment is dependent on the choice of reporter. Researchers must also account for developmental age and disease; in assessing generic and disease-specific functioning, the ''functional scale'' against which an individual is compared must implicitly reflect the types of activities and/or levels of functioning that are realistic norms for the patient. Equally important is the analysis of independent domains in order to characterize the dynamics/divergence of clinical status and functional status.

What are the merits of conducting QOL research for the pediatric cancer-survivor population? The policy implications are profound and pervasive both for the individual survivors (regarding treatment, care, and his/her ultimate ability to reintegrate into society) and for society (regarding resource allocation, cost planning, and productivity). Commensurate with the rapid advancement of oncologic therapy, there is now an expanding cohort of pediatric cancer survivors. Current estimates suggest that, by the turn of the century, 200,000 children will be in this category. The long-term survivorship of this cohort is still poorly defined. However, as the survivors mature, it is likely that their needs will evolve as well–whether for treatment of secondary malignancies, long-term morbidities, and fertility issues or for neuropsychological dysfunction, emotional counseling, or occupational issues. Children, as survivors, are unique, in that their future (the context within which long-term outcome is defined) spans decades. Based on a median age at diagnosis of 6 years, survivors can expect to live an additional 66 years. From a cost or policy perspective, children represent enormous future potential. The implications of children's long-term outcomes must be considered regarding the change in future potential secondary to survivorship.

Pediatric QOL research plays a role both inside and outside the health care system. Clearly, in the provision of health care, QOL data may be used to improve or modify patient care by supplementing information about the clinical status of individual patients. Information about an individual's general functioning, particularly as it diverges from disease-specific functioning, complements clinical data to facilitate comprehensive care. Information about the long-term outcomes of pediatric cancer, as a whole, will influence the policies of health care institutions and the allocation of health care resources. By expanding the scope of survivorship (or cure) to include long-term clinical and general ''costs,'' the ''cost of cure'' is shifted: this shift will ultimately impact estimations of cost effectiveness, with ramifications for the evaluation of hospital-wide protocols, utilization priorities, and cost policies. Outside of the hospital, the implications of QOL research are equally ubiquitous. Pediatric survivors will live an estimated 7 decades after ''cure,'' during which time they will exist almost entirely outside the realm of health care; yet, their condition as a survivor, with or without the long-term clinical toxicities secondary to treatment, will continue to affect some or all of their abilities to function. Some survivors clearly have special needs, whether they are physical, cognitive, or emotional, that can influence their ability to lead normal, productive lives. *All* survivors suffer the stigmatizing effects of their survivorship that impact on fundamental areas, such as employment, insurability, and relationships. QOL research will help clarify these needs, maximizing the allocation of resources (education, psychological or occupational therapy) as well as shaping activities of daily living.

Pediatric QOL is a methodological conundrum, a challenge that is driven in large part by the complexity of assessing children and childhood. Given the enormous importance of this work, however, it is a challenge that can and will be met.

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REFERENCES

1. Brown RT, Madan-Swain A, Pais R, et al.: Chemotherapy for acute lymphocytic leukemia: Cognitive and academic sequelae. J Pediatr 121(6):885–889, 1992.
2. Mulhern RK, Wasserman AL, Fairclough D, et al.: Memory function in disease-free survivors of childhood acute lymphocytic leukemia given CNS prophylaxis with or without 1800 cGy cranial irradiation. J Clin Oncol 6(2):315–320, 1988.
3. Mulhern RK, Wasserman AL, Friedman AG, et al.: Social competence and behavioral adjustment of children who are long-term survivors of cancer. Pediatrics 83(1):18–25, 1989.
4. Williams KS, Ochs J, Williams JM, et al.: Parental report of everyday cognitive abilities among children treated for acute lymphoblastic leukemia. J Pediatr Psychol 16(1):13–26, 1991.
5. Rubenstein CL, Varni JW, Katz ER: Cognitive functioning in long-term survivors of childhood leukemia: A prospective analysis. J Dev Behav Pediatr 11(6):301–305, 1990.
6. Deasy-Spinetta P, Spinetta JJ: The child with cancer in school: Teacher's appreciation. Am J Pediatr Hematol-Oncol 2(1):89–94, 1980.
7. Jannoun L, Chessels JM: Long-term psychological effects of childhood leukemia and its treatment. Pediatr Hematol-Oncol 4: 292–308, 1987.
8. Barr RD, Furlong W, Dawson S, et al.: An assessment of global health status in survivors of acute lymphoblastic leukemia in childhood. Am J Pediatr Hematol-Oncol 15(3):284–290, 1993.
9. Mulhern RK, Fairclough DL, Smith B, et al.: Maternal depression,

assessment methods, and physical symptoms affect estimates of depressive symptomatology among children with cancer. J Pediatr Psychol 17(3):313–326, 1992.
10. Rey JM, Schrader E, Morris-Yates A: Parent-child agreement on children's behaviours reported by the child behaviour checklist (CBCL). J Adolesc 15:219–230, 1992.
11. Achenbach TM, McConaughy SH, Howell CT: Child/adolescent behavioural and emotional problems: Implications of cross-informant correlations for situational specificity. Psychol Bull 101:213–232, 1987.
12. Merkens MJ, Perrin EC, Perrin JM, et al.: The awareness of primary physicians of the psychosocial adjustment of children with a chronic illness. Dev Behav Pediatr 10(1):1–6, 1989.
13. Perrin EC, West PD, Culley BS: Is my child normal yet? Correlates of vulnerability. Pediatrics 83(3):355–363, 1989.
14. Sanger MS, MacLean WE Jr, Van Slyke DA: Relation between maternal characteristics and child behavior ratings. Implications for interpreting behavior checklists. Clin Pediatr 31(8):461–466, 1992.
15. Perrin EC, Ayoub CC, Willett JB: In the eyes of the beholder: Family and maternal influences on perceptions of adjustment of children with a chronic illness. Dev Behav Pediatr 14(2):94–105, 1993.
16. Mechanic D: The influence of mothers on their children's health attitudes and behavior. Pediatrics 33(3):444–453, 1994.
17. Testa MA, Simonson DC: Assessment of quality of life outcomes. New Engl J Med 334(13):835–840, 1996.
18. Guyatt GH, Veldhuyzen Van Zanten SJ, Feeney DH, et al.: Measuring quality of life in clinical trials: a taxonomy and review. Can Med Assoc J 140:1441–1448.
19. Schipper H, Levitt M: Measuring quality of life : Risks and benefits. Cancer Treat Rep 69(10):1115–1123, 1985.
20. Ware JE, Sherbourne CD: The MOS 36-Item Short-Form Health Survey (SF-36) I. Conceptual framework and item selection. Med Care 30:473–483, 1992.
21. McHorney CA, Ware JE, Raczek AE: The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 31(3):247–263, 1993.
22. Bergner M, Bobbitt RA, Pollard WE, et al.: The Sickness Impact Profile: Validation of a health status measure. Med Care 14:57–67, 1976.
23. Morrow GR, Feldstein M, Adler LM, et al.: Development of brief measures of psychosocial adjustment to medical illness applied to cancer patients. Gen Hosp Psychol 3:79–81, 1981.
24. Achenbach TM, Edelbrook CS: ''Manual for the Child Behaviour Checklists and Revised Child Behaviour Profile.'' Burlington, VT: Department of Psychiatry, University of Vermont, 1983.
25. Walker DK, Stein RE, Perrin EC, et al.: Assessing psychosocial adjustment of children with chronic illness: A review of the technical properties of PARS III. Dev Behav Pediatr 11(3):116–121, 1990.
26. Gesten EL: A Health Resources Inventory. J Consult Clin Psychol 44:775–780, 1964.
27. Perrin EC, Stein REK, Drotar D: Cautions in using the child behavior checklist: Observations based on research about children with a chronic illness. J Pediatr Psychol 16(4):411–421, 1991.
28. Cella DF: Methods and problems in measuring quality of life . Support Care Cancer 3:11–22, 1995.
29. Shipper H, Clinch J, McMurray A, et al.: Measuring the quality of life of cancer patients: The Functional Living Index–Cancer: Development and validation. J Chron Dis 34:472–483, 1984.
30. Cella DF, Tulsky DS, Gray G, et al.: The Functional Assessment of Cancer Therapy Scale: Development and validation of the general measure. J Clin Oncol 11(3):570–579, 1993.
31. Aaronson NK, Ahmedzai S, Bergman B, et al., for the European Organization for Research and Treatment of Cancer Study Group on Quality of Life: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality of life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376, 1993.
32. Spitzer WO, Dobson AH, Hall J, et al.: Measuring the quality-of-life in cancer patients: A concise quality of life index for use by physicians. J Chron Dis 34:585–597, 1981.
33. Apgar V: Proposal for new methods of evaluation of newborn infants. Anesthesiol Anal 32:260, 1953.
34. Goodwin DA, Boggs SR, Graham-Pole J. Development and validation of the Pediatric Oncology Quality of Life Scale. Psychol Assess 6:321–328, 1994.
35. Feeny D, Furlong W, Barr RD, et al.: A comprehensive multiattribute system for classifying the health status of survivors of childhood cancer. J Clin Oncol 10(6):923–928, 1992.
36. Karnofsky DA, Bucheral JH: The clinical evaluation of chemotherapeutic agents in cancer. In MacLeod CM (ed): ''Evaluation of Chemotherapeutic Agents.'' New York: Columbia University Press, 1949, pp. 1191–205.
37. Lansky SB, List MA, Lansky LL, et al.: The measurement of performance on childhood cancer patients. Cancer 60:1651–1656, 1987.
38. Feeny D, Barr RD, Furlong W, et al.: Quality of life of the treatment process in pediatric oncology: An approach to measurement. In Osoba D (ed): ''Effect of Cancer on Quality of Life.'' Boca Raton, FL: CRC Press, Inc., 1991, pp. 74–88.
39. Ganz PA, Lee JJ, Siau J: Quality of life assessment. An independent prognostic variable for survival in lung cancer. Cancer 67: 3131–3135, 1991.
40. Coates A, Gebski V, Signorini D, et al., for the Australian New Zealand Breast Cancer Trial Group: Prognostic value of quality of life scores during chemotherapy for advanced breast cancer. J Clin Oncol 10:1833–1838, 1992.
41. Addington-Hall JM, MacDonald LD, Anderson HR: Can the Spitzer quality of life index help to reduce prognostic uncertainty in terminal care? Br J Cancer 62:695–699, 1990.